PCT/GB 99 / 03 302

The Patent Office

15 OCTOBER 1999

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

EJV

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Signed Andrew Gervey

Dated 26 October 1999

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
A
15 OCT 1998
RECEIVED BY FAX

The Patent Office

15 OCT 1998

9
15OCT98 E397425-1 D02866
P01/7700 0.00 - 9822459.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

ICOW\P19054GB

2. Patent application number
(The Patent Office will fill in this part)

9822459.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Imperial College Innovations Limited
Sherfield Building
Imperial College
London SW7 2AZ
United Kingdom

Patents ADP number *(if you know it)*

7409436002

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

METHOD OF TREATMENT

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

ERIC POTTER CLARKSON
PARK VIEW HOUSE
58 THE ROPEWALK
NOTTINGHAM
NG1 5DD

Patents ADP number *(if you know it)*

1305010

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	18 / p2
Claim(s)	0
Abstract	0
Drawing(s)	5 /

10. If you are also filing in any of the following, state how many against each item.

Priority Documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	NO
Request for preliminary examination and search *(Patents Form 9/77)*	NO
Request for substantive examination *(Patents Form 10/77)*	NO
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson Date 15 October 1998

ERIC POTTER CLARKSON

12. Name and daytime telephone number of person to contact in the United Kingdom 0115 9552211

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 01645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

METHOD OF TREATMENT

The present invention relates to a method of treatment of cachexia.

Cachexia is a severe complication of several chronic diseases, including chronic heart failure (CHF), malignant cancer, acquired immunodeficiency syndrome, thyrotoxicosis and rheumatoid arthritis. The prognostic importance of wasting is well established in several of these conditions [1,2,3]. In a single-center study with a total of 171 CHF patients, we documented for the first time that weight loss in CHF is linked to impaired survival independently of other well recognised risk factors (e.g. New York Heart Association [NYHA] functional class, peak oxygen consumption, and left ventricular ejection fraction [LVEF]) [4]. Although prospective in design, this study was of limited size, the definition of cardiac cachexia employed (>7.5% documented weight loss) was arbitrary, and it was performed in a research-oriented tertiary referral center with potentially highly selected patients. To date it is not known how frequently significant weight loss occurs in a large unselected population of CHF patients, and when occurring what prognostic impact it carries. It seems logical to define the presence of wasting on the basis of documented weight loss [5]; the degree of weight loss best linked to impaired survival is not known.

Multiple physiological pathways are disordered in CHF, and a series of vicious cycles have been discribed that could transform cardiac abnormalities into hemodynamic, endocrine, immunological, and muscular abnormalities that all could, in the turn, contribute to the clinical picture of chronic heart failure [6,7,8,9]. The relative contributions of these very different pathways may vary - not only from patient to patient, but also with each individual over time. The best studied and most widely available treatment option with a positive effect on symptoms and survival of CHF patients is treatment with angiotensin converting enzyme (ACE) inhibitors. It is increasingly evident that ACE inhibitors exert beneficial effects beyond simple hemodynamic effects via a variety of pathways. These include beneficial effects on the neurohormonal axis [10] and the endothelium [11]. The effect of ACE inhibitors on the development of cachexia is however unknown. The survival benefit of patients with CHF treated with enalapril vs placebo in CONSENSUS [12] and vs hydralazine-isosorbide dinitrate in V-HeFT II [13] is only significantly achieved in patients with increased catecholamine levels, i.e. in patients with normal levels no significant survival benefit was seen. We have recently

documented [14] that in contrast to peak VO_2, LVEF, or NYHA class, raised catecholamine levels were closely related to the presence of cardiac cachexia. If ACE inhibitors exert particularly beneficial effects in heart failure patients with raised catecholamine levels, and if these patients are more frequently cachectic, we hypothesised, that the beneficial effect of ACE inhibitors might be linked to a beneficial effect on cardiac cachexia.

To explore these questions and hypotheses, we have performed a re-analysis of the patients treated in the SOLVD treatment trial [15]. To avoid problems related to weight loss due to reduction of edema present at baseline, the results presented here are based on those 2082 patients that were free of detectable peripheral edema at baseline. The reliable quantification of edema is difficult . To avoid biasses inherent in estimating weight loss in patients who could also have developed edema we did not adjust for the development of edema during follow-up. Therefore the data presented in this study can be regarded as conservative estimates with regard to the frequency of weight loss, for in the presence of new edema our estimates of weight loss would always be underestimates.

METHODS

Patient population

We report on CHF patients who participated in the SOLVD treatment trial [15]. The SOLVD treatment study was a randomized, double blind, and placebo-controlled trial investigating the effects of enalapril treatment in clinically stable patients with a LVEF of 35% or less and evidence of overt congestive heart failure. The precise details of study organisation, inclusion criteria, run-in period (2 to 7 days) and stabilization period (14 to 17 days), randomisation, treatment titration and follow-up have been reported previously [15]. The current re-analysis is restricted to subjects who participated in the SOLVD treatment trial (n=2569), and who had been free of edema at baseline and had survived for at least 4 months thereafter (n=2090). For inclusion into the analysis we also required patients to have weight measurements at baseline

and from at least one follow-up visit at 4 months or later. A further 8 subjects with missing or invalid values for weight measurements had to be excluded. The final number of subjects included in this report is 2082 (81.04% of the original trial population). The baseline clinical characteristics of these 2082 patients were not significantly different from the characteristics of the total study population.

Treatment and follow-up

Of the 2082 patients, 1055 patients were randomised to treatment with enalapril (2.5 to 20mg per pay) and 1027 patients to treatment with placebo. The clinical characteristics of these two groups were also similar at baseline (Table 2). During follow-up (range 22 to 51 months), and a total of 756 deaths were observed (36.3%). Body weight at baseline and during follow-up was measured per protocol. Body height was not recorded.

Statistical analysis

Comparison of means between groups was carried out using an unpaired t-test. Comparison of proportions between groups was made by employing the chi-square test. With regards to the definition of the presence of cachexia different, a priori suggested, cut-points [16] of 5.0%, 7.5%, 10.0% and 15.0% weight loss were considered. To address the question of whether or not ACE inhibitors influence the risk of first occurrence of cachexia, we plotted the cumulative incidence of cachexia in the two treatment groups, and analysed it employing the log-rank statistic [17]. In the analysis of first occurrence of cardiac cachexia, at any given follow-up visit, absence of information on cardiac cachexia (i.e. weight not documented at this visit) is treated as censored. The effect of cardiac cachexia on survival is assessed using Cox proportional hazard analysis [16]. For these analyses cardiac cachexia is treated as a time-dependent covariate. The assessment of cardiac cachexia at 4, 8, and 12 months was used in the analysis. These are the time points in the follow-up period with relatively high proportion of complete information on

cachexia status. In the database, information on cachexia status is very sparse towards the end of follow-up, which makes it difficult to assess cardiac cachexia as "truly" time-dependent.

The primary analysis was intention-to-treat. Statistical significance is claimed at a computed p-value <0.05 (two-sided testing). Estimates of effects are provided along with their 95% confidence intervals. Results are adjusted for a priori identified prognostic factors such as age, gender, NYHA functional class, LVEF (_25% or >25%), and treatment status (enalapril vs placebo, in the case of assessing the effect of cardiac cachexia on survival).

RESULTS

Of the 2082 CHF patients in this study, 657 (31.6%) developed _7.5% weight loss during follow-up. The cumulative frequency of cardiac cachexia increased continuously over time (Figure 1). The frequency of _7.5% weight loss (cross-sectional) at 1 year was 8.5% and it increased to 15.5% (2 years), and 17.2% (3 years). At baseline patients who developed cardiac cachexia with _7.5% weight loss during follow-up were 1.3 years older (mean 61.2 vs 59.9, p<0.01), had 2.7 kg higher weight (mean 80.5 vs 77.8 kg, p<0.001), and they were slightly more frequently treated with diuretics (87.2 vs 82.6%, p<0.01) (Table 1). Of the patients in this study, 375 (18.0%) were female. Female CHF patients developed cardiac cachexia more frequently (39.5% vs 29.8% in males for _7.5% weight loss, p<0.001). Otherwise the baseline clinical characteristics, particularly with regards to NYHA class, LVEF, and disease etiology, of patients who developed cardiac cachexia and those who did not were similar (Table 2). The following clinical characteristics at baseline were independently related to the subsequent development of cardiac cachexia: age (RR , p<0.001), NYHA class (), LVEF, and treatment ().

Cardiac cachexia and survival

The development of cardiac cachexia was closely related to subsequently impaired survival. All a priori identified competitive cut-points for cardiac cachexia were related to impaired survival - independent of the effects of age, gender, NYHA class, LVEF, and treatment allocation. Of the 756 deaths observed during follow-up, 223 occurred in patients who had been classified as cachectic (_7.5% weight loss) at the last visit prior to death, i.e. 29.5% of deaths in CHF patients occurred with cardiac cachexia being present. Amongst different cut-offs for cardiac cachexia between 5 and 15%, weight loss _6.5% was the strongest predictor of impaired mortality. The crude effect of cachexia (weight loss _6.5%) on survival was highly significant: RR 1.47 (95% confidence interval: 1.27 to 1.70), p=0.00000017.

Cardiac cachexia and ACE inhibitor treatment

Patients who were allocated to treatment with enalapril had a significantly lower risk of developing cardiac cachexia during follow-up (Figure). The crude effect of treatment allocation with enalapril was significantly related to a reduced risk of developing cardiac cachexia: RR 0.81 (95% confidence interval: 0.70 to 0.95), p=0.0085. Treatment allocation to enalapril had a significantly beneficial effect on survival independently of the effect of age, gender, NYHA class, and LVEF also in this subset of patients of the SOLVD treatment trial ($p<0.01$). When we adjusted also for the presence of cardiac cachexia (6.5% weight loss) at 4 or 8 months, the treatment effect remained significant. In patients who developed weight loss _7.5% at any time point, only 10 patients with subsequently recorded weights equal to or higher than the baseline weight were found (enalapril group: 6, placebo: 4).

DISCUSSION

This report has demonstrated that significant weight loss, i.e. cardiac cachexia, is a frequent event in CHF patients. Weight loss _7.5% occurs in about 1/3 of patients over 3 years. Spontaneous reversal of the weight loss is a very rare event occurring in less than 2% of cases. Cardiac cachexia is closely and independently linked to impaired survival of CHF patients.

Treatment with an angiotensin converting enzyme inhibitor, enalapril, in addition to conventional therapy reduced the frequency of the risk of death and the risk of developing cardiac cachexia. Overall, enalapril therapy reduced the risk of developing cardiac cachexia by 19%.

It can be estimated that treatment with enalapril delayed the development of cardiac cachexia by about 7 months during the first 3 years. Interestingly, from the SOLVD treatment trial [15] it can be estimated that enalapril delayed the occurrence of death events on average by 5.4 months. A precise estimate of the proportion of the survival benefit of enalapril that was mediated through its benefit on the occurrence of body wasting is not possible to quantify, but the results of the statistical analyses show that at least some of the mortality benefit of angiotensin-converting enzyme inhibitors is mediated through the prevention or delay of cardiac cachexia.

This is the first study to analyse the frequency and degree of weight loss in CHF patients in relation to a therapeutic intervention (not considering studies with diuretics in edematous patients), and therefore we can not compare the preventive effect of enalapril on cardiac cachexia to results of other published studies. Spontaneous reversal of cardiac cachexia seems to be a very rare observation. In our own experience with about 50 patients with cardiac cachexia, we observed only of one case of spontaneous weight gain and long-term survival, and 3 cases of long-term weight stability and survival (>4 years). From clinical experience it is known that cardiac cachexia can be reversed after heart transplantation or implantation of left ventricular assist devices, but this has never been studied in detail. The present study is only the second study to analyse weight loss frequency and its prognostic impact. Previously [4] we have reported that cachectic patients with >7.5% weight loss occur with a cross-sectional frequency of 16.4%, compared to the 15 to 17% seen after 2 to 3 years in this report. With respect to cross-sectional frequency of cachexia, and the prognostic independence (from age, LVEF, and NYHA class) the present much larger multi-center study confirmed our previous findings.

In the present study population 30% of all deaths occurred on the background of newly developed cardiac cachexia - this is in a population were patients were considered clinically stable and non-cachectic at baseline. We have estimated that in our previously studied population [4] with 16.4% prevalence of cardiac cachexia at baseline nearly 50% of all deaths over a period of 18 months were related to body wasting [18]. Previous large randomised treatment trials in CHF patients did not assess the history of weight loss at baseline, have not reported weight changes over time, excluded patients with significant weight changes during the stabilisation period (V-HeFT II), or did not even report body weight at baseline [19]. Body height and body mass index are reported only rarely. Also in the SOLVD studies height has not been recorded - therefore this study reports only on absolute weight changes within patients, that are thought to be the core characteristic of the wasting disease.

Originally, treatment with angiotensin converting enzyme inhibitors has been introduced on the basis of hemodynamic considerations [20], although it was then also suggested that vasodilators per se do not have independent prognostic value, but rather that ACE inhibitors appear to be beneficial [21] perhaps via their neurohormonal antagonistic effects. The smallest randomised controlled trial of drug treatment in CHF patients with adequate power and positive mortality results was the CONSENSUS study [22], with 253 patients in NYHA class IV and a mean follow-up of only 188 days, where enalapril caused a mortality risk reduction of 27% ($p=0.003$). In this study body weight at baseline was about 11 kg lower then in the present study - cachexia may have been relatively frequent in these patients. It could be hypothesised that due to metabolic effects angiotensin converting enzyme inhibitors have most powerful effects in patients with particularly advanced heart failure and in patients at risk of developing cachexia. In this context it is important that it has been noted that a significant survival benefit of patients with CHF treated with angiotensin converting enzyme inhibitors is only seen in patients with increased catecholamine levels [12,13]. Raised catecholamine levels are not only a prominent feature of cachectic CHF patients [14], but they can also contribute to upregulation of resting metabolic rates [23], that have been found in CHF patients [24].

Cardiac cachexia forms a distinct metabolic disease developing on the background of heart failure. Prevention of cachexia by treatment with the angiotensin converting enzyme inhibitor, enalapril, may indicate an important mode of action of this drug and may illustrate the importance of metabolic pathways for the progression of heart failure for its optimum therapy.

REFERENCES

1. Kotler DP, Tierney AR, Wang J, Pierson RN Jr. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. Am J Clin Nutr 1989;50:444-447.

2. Chlebowski RT, Grosvenor MB, Bernhard NH, Morales LS, Bulcavage LM. Nutritional status, gastrointestinal dysfunction, and survival in patients with AIDS. Am J Gastroenterol 1989;84:1288-1293.

3. Souhami RL. Cancer: clinical features and management. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. Oxford textbook of medicine. Third edition. Oxford: Oxford University Press 1996: 240-242.

4. Anker SD, Ponikowski P, Varney S, Clark AL, Chua TP, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJS. Wasting as independent risk factor of survival in chronic heart failure. Lancet 1997;349:1050-1053.

5. Anker SD, Coats AJS. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999. (in press)

6. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248-254.

7. Anker SD, Clark AL, Kemp M, Salsbury C, Teixeira MM, Hellewell PG, Coats AJS. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. J Am Coll Cardiol 1997;30:997-1001.

8. Coats AJS, Clark AL, Piepoli M, Volterrani M, Poole-Wilson PA. Symptoms and quality of life in heart failure; the muscle hypothesis. Br Heart J 1994;72:S36-S39.

9. Anker SD, Egerer K, Volk H-D, Kox WJ, Poole-Wilson PA, Coats AJS. Elevated soluble CD14 receptors and and altert cytokines in chronic heart failure. Am J Cardiol 1997;79:1426-1430.

10. Anker SD. Catecholamine levels and treatment in chronic heart failure. Europ Heart J 1998 (Suppl F);19:F56-F61.

11 Hornig B, Arakawa N, Drexler H. Effect of ACE inhibition on endothelial dysfunction in patients with chronic heart failure. Eur Heart J 1998;19 (Suppl G):G48-53.

12. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group.Circulation 1990;82:1730-1736.

[13]. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group.Circulation 1993;87 (Suppl VI):VI40-VI48.

[14]. Anker SD, Chua TP, Swan JW, Ponikowski P, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJS. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure: The importance for cardiac cachexia. Circulation 1997;96:526-534.

[15]. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

[16]. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society 1972;B34:187-220.

[17]. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley and Sons Inc, 1980.

[18]. Anker SD, Coats AJS. Cachexia in heart failure is bad for you. Europ Heart J 1998;19:191-193.

[19]. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure. Lancet 1997;349:747-752.

[20]. Lipkin DP, Poole-Wilson PA. Treatment of chronic heart failure: a review of recent drug trials. Br Med J 1985;291:993-996.

[21]. Furberg CD, Yusuf S. Effect of vasodilators on survival in chronic congestive heart failure. Am J Cardiol 1985;55:1110-1113.

[22]. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

[23]. Poehlman ET, and Danforth E. Endurance training increases metabolic rate and norepinephrine appearence rate in older individuals. Am J Physiol 1991;261:E233-E239.

[24] Poehlmann ET, Scheffers J, Gottlieb SS, Fisher ML, and Vaitekevicius P. Increased resting metabolic rate in patients with congestive heart failure. Ann Intern Med 1994;121:860-862.

The invention includes a method of treating a patient who has or who is at risk of cachexia the method comprising administering to the patient an effective amount of an inhibitor of the renin-angiotensin system (RAS). Such inhibitors include, but are not limited to, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor (particularly ATII) anatagonists. Both of these classes of inhibitors are well known in the art and some of them are listed for example in the latest edition of the British National Formulary and in the latest edition of Martindale's Pharmacopeia.

ACE inhibitors include alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fosinopril, lisinopril, moexipril, and the like. A particularly preferred ACE inhibitor is enalapril. Angiotensin receptor antagonists include candesartan, eprosartan, losartan, valsartan and the like. A particularly preferred angiotensin receptor anatagonist is losartan.

The RAS inhibitor is administered to the patient in any suitable form and in a dose which has the desired effective of reducing or preventing cachexia.

The invention also includes the use of a RAS inhibitor in the manufacture of a medicament for treating or preventing cachexia.

Cachexia may be due to underlying disease, and it may be useful to treat the patient for the underlying disease as well as treating the cachexia according to the invention. Underlying diseases which may lead to cachexia include, for example, AIDS, liver cirrhosis, chronic obstructive pulmonary disease with or without emphysema, chronic renal failure, chronic infections (like pneumonia), cancer, heart disease including hypertension and chronic heart failure and idiopathic cachexia.

ANKER 1. DOC

Example:

Exemplification of treatment of cachexia patients with an AT II receptor antagonist (Losartan).

(renin - angiotensin system)

We propose that the blockade of the RAS is of benefit for cachectic patients - even if such patients are previously treated with an ACE inhibitor. To exemplify this, we have treated 1 patient with cachexia due to chronic heart failure (CHF) (age 74 years, male, weight 50.0 kg, height 178 cm, previous weight loss 15.3 kg in 3 years = chronic weight loss) and 1 patient with CHF and a muscle myopathy suffering from idiopathic cachexia (age 38 years, male, weight 62 kg, height 180 cm, previous weight loss 11 kg in 1 year = recent weight loss) with Losartan (50 mg once daily) and we have studied clinical status and parameters of body composition, strength and treadmill exercise capacity at baseline and during follow-up. Both patients had evidence of CHF with impaired exercise capacity and impaired left ventricular function (LVEF <40%). Both patients had a good compliance.

Used Methods:

1. Bioelectrical impedance analysis (patient 1 and 2) was performed in the erect position using a body fat analyser (TANITA TBF-305, Tanita Corporation, IL, USA). Lean and fat mass were automatically analysed based on equations supplied and programmed into the machine by the manufacturer. These equations are based upon a comparison with measurements in a healthy population.
2. Dual energy x-ray absorptiometry (DEXA) (patient 1): Whole body DEXA-scans were performed in the Royal Brompton Hospital, London using a Lunar model DPXIQ total body scanner (Lunar Radiation Company, Madison, WI, USA, Lunar system software version 4.3c). The subject was at each time point scanned rectilinearly from head to toe. A scan takes less than 20 min. The mean radiation dose per scan is reported to be about 0.75 µSv [1], about 1/50th of a normal chest x-ray. The DEXA method can be used to obtain from body density analyses values of fat tissue mass, lean tissue mass. The technical details of DEXA, performance and segment demarcation have been described by Mazess et al [2,3]. The error of lean tissue measurements is <2% and of fat tissue measurements <5% [4].
3. Treadmill exercise test (patient 1 and 2): The patients underwent symptom limited treadmill exercise testing. A standard Bruce protocol with the addition of a "stage 0" consisting of 3 min at a speed of 1 mile per hour with a 5% gradient was used. The patients breathed through a one-way valve connected to a respiratory mass spectrometer (Amis 2000, Odense, Denmark) and minute ventilation, oxygen consumption and carbon dioxide production were calculated on line every 10 seconds using a standard inert gas dilution technique. Patients were encouraged to exercise to exhaustion. Exercise time and oxygen consumption at peak exercise adjusted for total body weight (peak VO_2 in ml/kg/min) were measured as an index of the exercise capacity.
4. Assessment of quadriceps muscle strength (patient 1 and 2): The subjects were seated in a rigid frame, with the legs hanging freely. An inelastic strap attached the ankle to a pressure transducer. The recording (Multitrace 2, §, Jersey, Channel Islands) from the pressure transducer was used to

assess strength and to provide visual feedback to the subject. A plateau of maximum force production indicated that the contraction was maximal. The best of three voluntary contractions on each leg, with a rest period of at least one minute in-between, was taken to represent the maximal voluntary quadriceps muscle strength of the right and left leg, respectively.

Results

The results are summarised in Table 1. We have data available on a follow-up of 126 days in patient 1 and 83 days in patient 2. Both patient were also studied at intermediate time points. Both patients improved during treatment by 1 NYHA symptom class. In both patients the exercise capacity improved during the study (exercise time: patient 1 and 2, peak VO_2: patient 2). There was evidence that in both patients quadriceps muscle strength improved in both legs. These clinical benefits were achieved on the background on a weight gain of 4.6 kg in patient 1 (lean and fat tissue gain), and by stopping the process of weight loss and apparently improving the general clinical status and relative muscle performance, i.e. muscle quality (patient 2). We observed no side effects of treatment.

References

1. Fuller NJ, Laskey MA, Elia M. Assessment of the composition of major body regions by dual-energy x-ray absorptiometry (DEXA), with special reference to limb muscle mass. Clinical Physiology 1992;12:253-266.

2. Mazess R, Collick B, Trempe J, Barden H, Hanson J. Performance evaluation of a dual-energy x-ray bone densiometry. Calcif Tissue Int 1989;44:228-232.

3. Mazess RB, Barden H, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone mineral and soft-tissue composition. Am J Clin Nutr 1990;51:1106-1112.

4. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body fat distribution. Am J Clin Nutr 1992;55:950-954.

Example: Treatment of a hypertensive patient with some weight loss previously

When the patient was assessed on 27 March 1998 (no ACE inhibitor) he weighed 74.6kg and had no oedema.

When assessed on 18 September 1998 following treatment with an ACE inhibitor he weighed 76.1 kg.

This shows that an ACE inhibitor can increase body weight in hypertensive patients besides their effect on lowering blood pressure.

A similar result was found in a second patient.

ANUK

Table 1

NYHA - New York Heart Association clinical classification of disease

Patient	study date	time point (days)	age (years)	NYHA class	peak VO2 (ml/kg/min)	exercise time (seconds)	Strength Right Leg (Newton)	Strength Left Leg (Newton)
1	02/06/98	baseline	74	4	patient to weak, exercise test and strength testing not possible			
1	11/06/98	9		4				
1	24/06/98	22		4				
1	14/07/98	42		3 to 4	8.2	84	147.15	153.41
1	25/08/98	84		3 to 4	8.6	138	223.52	228.73
1	06/10/98	126		3	machine broken - patient clinically much improved		198.27	214.59
2	09/07/98	baseline	38	3	14.4	329	85.30	79.22
2	25/08/98	48		2	15.6	335	124.91	109.67
2	30/09/98	83		2	17.9	380		

Patient	study date	time point (days)	DEXA lean kg	DEXA fat kg	DEXA fat %	Body weight	Fat % TANITA	Fat Mass (kg) TANITA	Lean Mass (kg) TANITA
1	02/06/98	baseline	44.112	2.466	5.3	50.00	Fat below 1 %, TANITA measurement not possible		
1	11/06/98	9				50.00	1.0	0.6	49.4
1	24/06/98	22	45.617	3.290	6.7	51.80	2.2	1.2	50.6
1	14/07/98	42				53.80	3.6	2.0	51.8
1	25/08/98	84				52.80	3.1	1.6	51.2
1	06/10/98	126	46.552	4.937	9.2	54.80	3.6	2.0	52.8
2	09/07/98	baseline				62.00	no TANITA performed		
2	25/08/98	48				62.20	11.5	7.2	55.0
2	30/09/98	83				63.30	10.5	6.4	54.8

Table 2

Table 13. Baseline characteristics

		Survival status		Treatment group		Cachexia	
N	2082	Alive 1326	Dead 756	Enalapril 1055	Placebo 1027	No 1425	Yes 657
Gender							
Female	375 (18.0)	261(19.7)	114 (15.1)‡	183 (17.3)	192 (18.7)	227 (15.9)	148 (22.5)‡
Male	1707 (82.0)	1065 (80.3)	642 (84.9)	872 (82.7)	835 (81.3)	1198 (84.1)	509 (77.5)
Age	60.3	59.7	61.4‡	60.1	60.5	59.9	61.2†
Weight	78.7	79.4	77.2‡	78.9	78.4	77.8	80.5‡
NYHA							
I	254 (12.2)	186 (14.0)	68 (9.0)†	132 (12.5)	122 (11.9)	181 (12.7)	73 (11.1)
II	1225 (58.7)	824 (62.1)	399(52.8)	619 (58.7)	604 (58.8)	852 (59.8)	371 (56.5)
III	582 (28.0)	308 (23.2)	274(36.2)	293 (27.8)	289 (28.1)	378 (26.5)	204 (31.1)
IV	23 (1.1)	8 (0.7)	15 (2.0)	11 (1.0)	12 (1.2)	14 (1.0)	9 (1.4)
EF							
> 25	1013 (48.7)	712 (53.7)	301 (39.8)†	511 (48.4)	502 (48.9)	687 (48.2)	326 (49.6)
≤ 25	1069 (51.3)	614 (46.3)	455 (60.2)	544 (51.6)	525 (51.1)	738 (51.8)	331 (50.4)
Diuretic							
No	332 (15.9)	234 (17.6)	98 (13.0)†	164 (15.5)	168 (16.4)	248 (17.4)	84 (12.8) †
Yes	1750 (84.1)	1092 (82.4)	658 (87.0)	891 (84.5)	859 (83.6)	1177 (82.6)	573 (87.2)
Antiarrhythmic							
No	1374 (66.0)	844 (63.7)	530 (70.1)†	708 (67.1)	666 (64.8)	930 (65.3)	444 (67.7)
Yes	708 (34.0)	482 (36.3)	226 (29.9)	347 (32.9)	361 (35.2)	495 (34.7)	213 (32.4)
Vasodilator							
No	954 (45.8)	623 (47.0)	331 (43.8)	502 (47.6)	452 (44.0)	654 (45.9)	300 (45.7)
Yes	1128 (54.2)	703 (53.0)	425 (56.2)	553 (52.4)	575 (56.0)	771 (54.1)	357 (54.3)
Etiology of HF							
Ischemic	1497 (72.0)	949 (71.7)	548 (72.6)	741 (70.2)	756 (73.8)	1023 (71.8)	474 (72.4)
Non-Ischemic	582 (28.0)	375 (28.3)	207 (27.4)	314 (29.8)	268 (26.2)	401 (28.2)	181 (27.6)
Cachexia							
No	1425 (68.4%)	892 (67.3%)	533 (70.5%)	741 (70.2%)	684(66.6%)	--	--
Yes	657 (31.6%)	434 (32.7%)	223 (29.5%)	314 (29.8%)	343(33.4%)		

* $p \le 0.05$, † $p \le 0.01$, ‡ $p \le 0.001$

For Tab 3

3

Table 3. Effect of Cachexia on Survival. Cachexia was assessed at 4 months of follow-up.

% weight-loss (at least)	Risk Ratio RR	95% CI	p
2.5 †			
Crude	1.29	(1.10, 1.50)	0.0016
Adjusted‡	1.28	(1.10, 1.49)	0.002
5.0			
Crude	1.35	(1.05, 1.75)	0.021
Adjusted	1.41	(1.10, 1.81)	0.006
7.5			
Crude	1.77	(1.20, 2.60)	0.004
Adjusted	2.08	(1.45, 2.99)	0.00007
10.0			
Crude	1.57	(0.85, 2.91)	0.15
Adjusted	1.70	(0.92, 3.16)	0.092
15.0			
Crude	9.08	(5.25, 15.7)	< 0.0001
Adjusted	8.78	(4.83, 15.95)	< 0.0001

precisely

† Cut-point for the definition of Cachexia at 4 months

‡Adjusted for age, treatment, gender, NYHA and ef

Increased risk of death with increased cachexia

Tab 3

4

Table 4B. Effect of Cachexia on Survival. Cachexia was assessed at 8 months of follow-up.

% weight loss (at least)	Risk Ratio RR	95% CI	p
2.5 †			
Crude	1.22	(1.04, 1.43)	0.014
Adjusted‡	1.21	(1.04, 1.42)	0.02
5.0			
Crude	1.42	(1.14, 1.76)	0.002
Adjusted	1.47	(1.18, 1.82)	0.0005
7.5			
Crude	1.66	(1.22, 2.26)	0.001
Adjusted	1.74	(1.28, 2.38)	0.00004
10.0			
Crude	1.62	(1.00, 2.63)	0.049
Adjusted	1.83	(1.14, 2.94)	0.013
15.0			
Crude	2.24	(0.96, 5.23)	0.062
Adjusted	2.53	(1.10, 5.83)	0.030

† Cut-point for the definition of Cachexia at 8 months

‡Adjusted for age, treatment, gender, NYHA and ef

Increased risk of death with increased cachexia

5

Table 3. Effect of Cachexia on Survival. Cachexia was assessed at each follow-up visit.

	RR	95% CI	P
Cachexia†	1.41	(1.23, 1.63)	<0.0001
Age	1.02	(1.01, 1.02)	<0.0001
Treatment	1.11	(0.96, 1.28)	0.170
Gender	1.34	(1.09, 1.65)	0.006
NYHAII	1.30	(0.99, 1.70)	0.06
NYHAIII	1.84	(1.39, 2.43)	<0.0001
NYHAIV	2.17	(1.33, 3.55)	0.002
EF	1.44	(1.23, 1.67)	<0.0001

† A 6.5 cut-point is used for the definition of Cachexia

Shows risk factors and their relation to predicting death independently of each other

Shows frequency of developing cardiocachexia over time is lower in patients treated with enalapril compared to patients treated with placebo

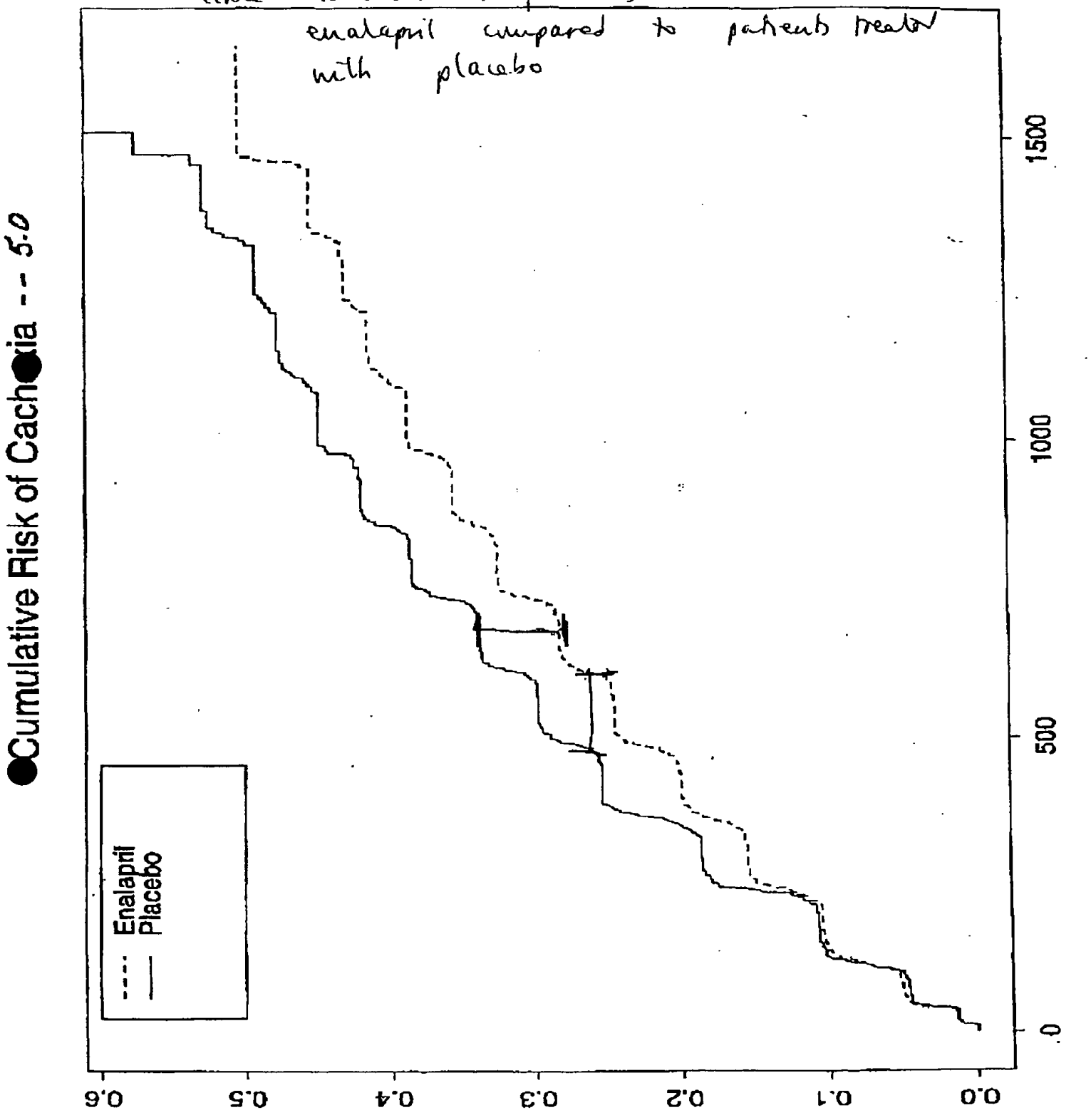


Figure 1

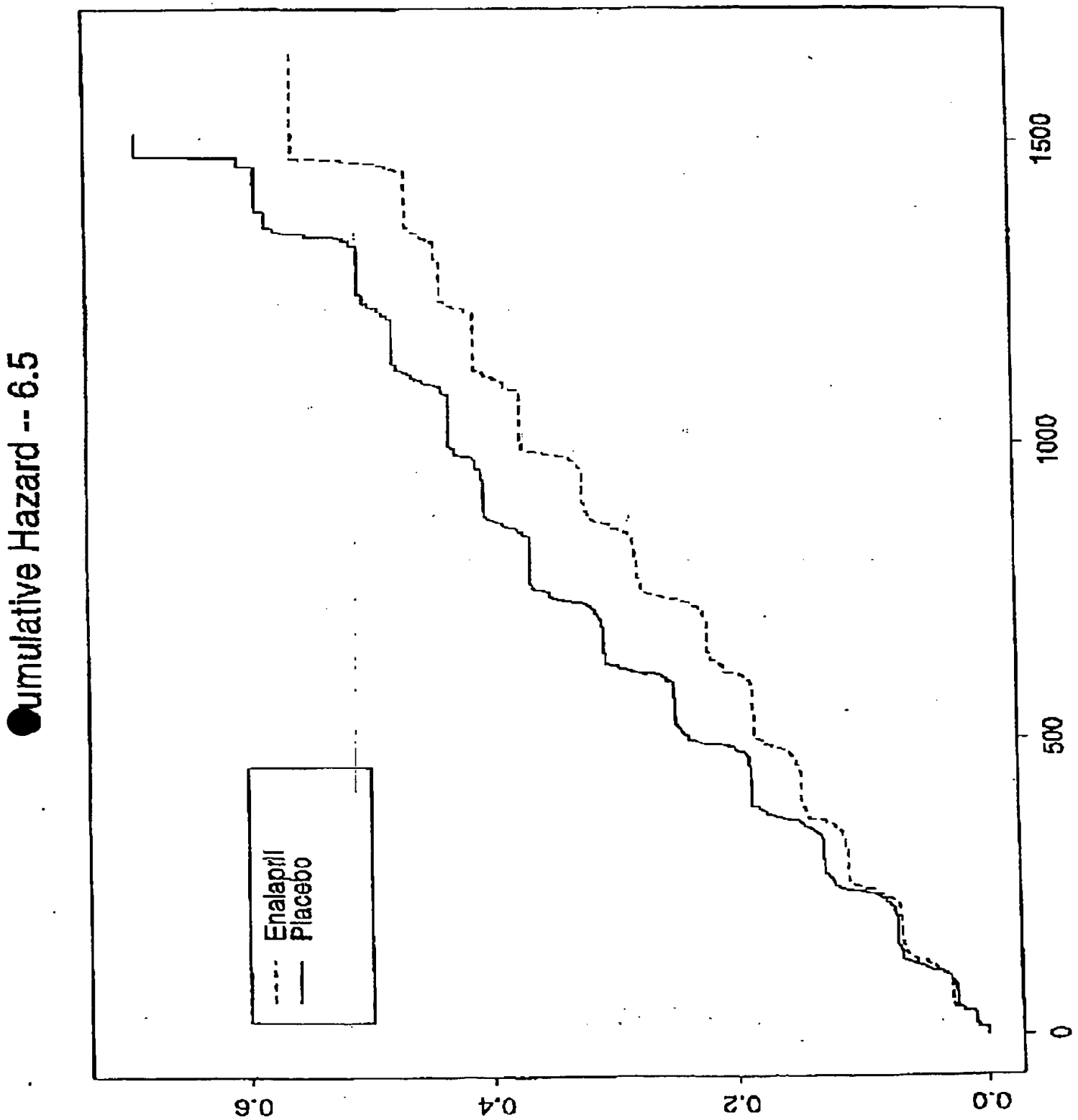

Cumulative Hazard -- 6.5
0.0
0.2
0.4
0.6
0
500
1000
1500
Enalapril
Placebo

Figure 2
215

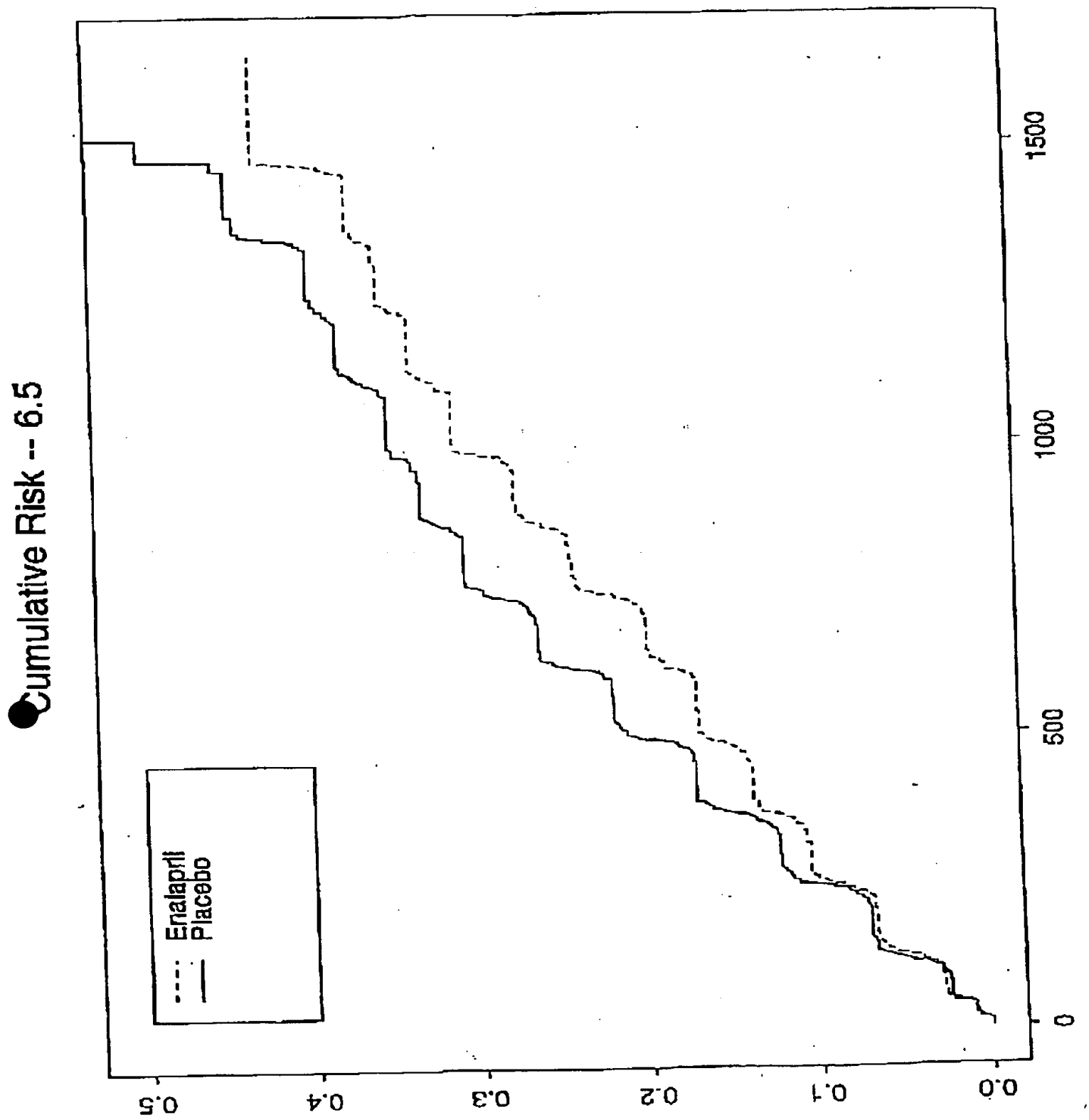


Figure 3

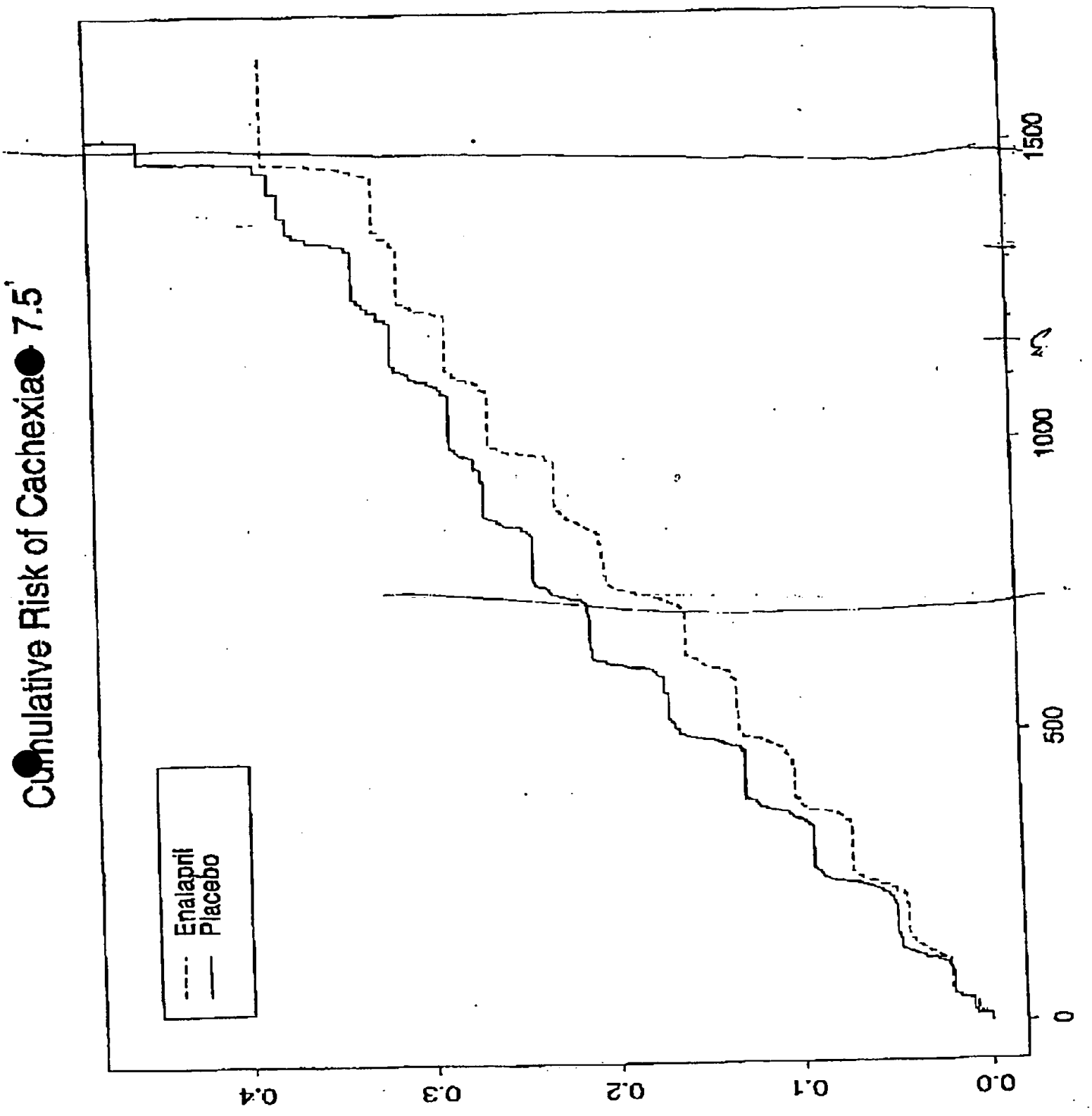
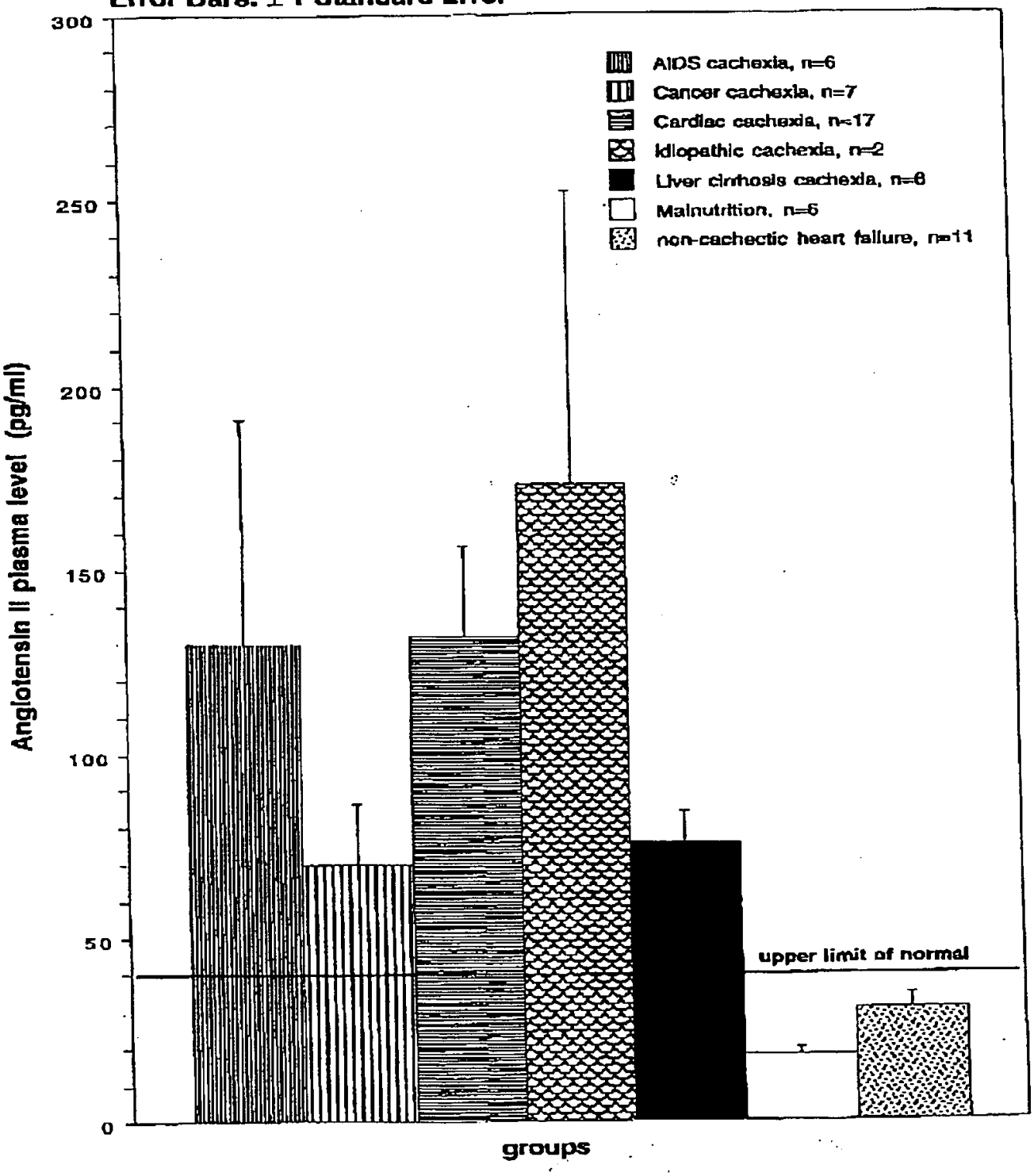

Cumulative Risk of Cachexia @ 7.5
Enalapril
Placebo
0.0
0.1
0.2
0.3
0.4
0
500
1000
1500

Figure 4

Angiotensin II plasma levels in various patient types



Patients with wasting disease have increased angiotensin II plasma levels.

Figure 5

PCT/GB99/03302

22/10/99

Eric Potter
clarkson